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<110> EXELIXIS, INC.

<120> MARKS AS MODIFIERS OF THE PTEN PATHWAY AND METHODS OF USE

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<150> US 60/479,768
<151> 2003-06-19

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Gly Gln Gln Lys Pro Leu Arg Val Gly Phe Tyr Asp Ile Glu Arg Thr
            20                  25                  30


Leu Gly Lys Gly Asn Phe Ala Val Val Lys Leu Ala Arg His Arg Val
        35                  40                  45


Thr Lys Thr Gln Val Ala Ile Lys Ile Ile Asp Lys Thr Arg Leu Asp
    50                  55                  60


Ser Ser Asn Leu Glu Lys Ile Tyr Arg Glu Val Gln Leu Met Lys Leu
65                  70                  75                  80


Leu Asn His Pro His Ile Ile Lys Leu Tyr Gln Val Met Glu Thr Lys
                85                  90                  95
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Asp Met Leu Tyr Ile Val Thr Glu Phe Ala Lys Asn Gly Glu Met Phe
            100                 105                 110

Asp Tyr Leu Thr Ser Asn Gly His Leu Ser Glu Asn Glu Ala Arg Lys
            115                 120                 125

Lys Phe Trp Gln Ile Leu Ser Ala Val Glu Tyr Cys His Asp His His
        130                 135                 140

Ile Val His Arg Asp Leu Lys Thr Glu Asn Leu Leu Leu Asp Gly Asn
145                 150                 155                 160

Met Asp Ile Lys Leu Ala Gly Thr Glu Asp Phe Gly Phe Gly Asn Phe
                165                 170                 175

Tyr Lys Ser Gly Glu Pro Leu Ser Thr Trp Cys Gly Ser Pro Pro Tyr
            180                 185                 190

Ala Ala Pro Glu Val Phe Glu Gly Lys Glu Tyr Glu Gly Pro Gln Leu
            195                 200                 205

Asp Ile Trp Ser Leu Gly Val Val Leu Tyr Val Leu Val Cys Gly Ser
    210                 215                 220

Leu Pro Phe Asp Gly Pro Asn Leu Pro Thr Leu Arg Gln Arg Val Leu
225                 230                 235                 240

Glu Gly Arg Phe Arg Ile Pro Phe Phe Met Ser Gln Asp Cys Glu Ser
                245                 250                 255

Leu Ile Arg Arg Met Leu Val Val Asp Pro Ala Arg Arg Ile Thr Ile
            260                 265                 270

Ala Gln Ile Arg Gln His Arg Trp Met Arg Ala Glu Pro Cys Leu Pro
        275                 280                 285

Gly Pro Ala Cys Pro Ala Phe Ser Ala His Ser Tyr Thr Ser Asn Leu
    290                 295                 300

Gly Asp Tyr Asp Glu Gln Ala Leu Gly Ile Met Gln Thr Leu Gly Val
305                 310                 315                 320

Asp Arg Gln Arg Thr Val Glu Ser Leu Gln Asn Ser Ser Tyr Asn His
            325                 330                 335

Phe Ala Ala Ile Tyr Tyr Leu Leu Leu Glu Arg Leu Lys Glu Tyr Arg
            340                 345                 350
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Asn Ala Gln Cys Ala Arg Pro Gly Pro Ala Arg Gln Pro Arg Pro Arg
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Ser Ser Asp Leu Ser Gly Leu Glu Val Pro Gln Glu Gly Leu Ser Thr
     370   375   380

Asp Pro Phe Arg Pro Ala Leu Leu Cys Pro Gln Pro Gln Thr Leu Val
385   390   395   400

Gln Ser Val Leu Gln Ala Glu Met Asp Cys Glu Leu Gln Ser Ser Leu
         405   410   415

Gln Trp Pro Leu Phe Phe Pro Val Asp Ala Ser Cys Ser Gly Val Phe
         420   425   430

Arg Pro Arg Pro Val Ser Pro Ser Ser Leu Leu Asp Thr Ala Ile Ser
     435   440   445

Glu Glu Ala Arg Gln Gly Pro Gly Leu Glu Glu Glu Gln Asp Thr Gln
     450   455   460

Glu Ser Leu Pro Ser Ser Thr Gly Arg Arg His Thr Leu Ala Glu Val
465   470   475   480

Ser Thr Arg Leu Ser Pro Leu Thr Ala Pro Cys Lys Phe Val Ser Pro
         485   490   495

Ser Thr Thr Ala Ser Pro Ala Glu Gly Thr Ser Ser Asp Ser Cys Leu
         500   505   510

Thr Phe Ser Ala Ser Lys Ser Pro Ala Gly Leu Ser Gly Thr Pro Ala
         515   520   525

Thr Gln Gly Leu Leu Gly Ala Cys Ser Pro Val Arg Leu Ala Ser Pro
     530   535   540

Phe Leu Gly Ser Gln Ser Ala Thr Pro Val Leu Gln Ala Gln Gly Gly
545   550   555   560

Leu Gly Gly Ala Val Leu Leu Pro Val Ser Phe Gln Glu Gly Arg Arg
         565   570   575

Ala Ser Asp Thr Ser Leu Thr Gln Gly Leu Lys Ala Phe Arg Gln Gln
         580   585   590

Leu Arg Lys Thr Thr Arg Thr Lys Gly Phe Leu Gly Leu Asn Lys Ile

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            595                    600                    605
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Lys Gly Leu Ala Arg Gln Val Cys Gln Ala Pro Ala Ser Arg Ala Ser
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Arg Gly Gly Leu Ser Pro Phe His Ala Pro Ala Gln Ser Pro Gly Leu
625   630   635   640

His Gly Gly Ala Ala Gly Ser Arg Glu Gly Trp Ser Leu Leu Glu Glu
                645   650   655

Val Leu Glu Gln Gln Arg Leu Leu Gln Leu Gln His His Pro Ala Ala
                660   665   670

Ala Pro Gly Cys Ser Gln Ala Pro Gln Pro Ala Pro Ala Pro Phe Val
                675   680   685

Ile Ala Pro Cys Asp Gly Pro Gly Ala Ala Pro Leu Pro Ser Thr Leu
        690   695   700

Leu Thr Ser Gly Leu Pro Leu Leu Pro Pro Pro Leu Leu Gln Thr Gly
705   710   715   720

Ala Ser Pro Val Ala Ser Ala Ala Gln Leu Leu Asp Thr His Leu His
                725   730   735

Ile Gly Thr Gly Pro Thr Ala Leu Pro Ala Val Pro Pro Pro Arg Leu
                740   745   750

Ala Arg Leu Ala Pro Gly Cys Glu Pro Leu Gly Leu Leu Gln Gly Asp
                755   760   765

Cys Glu Met Glu Asp Leu Met Pro Cys Ser Leu Gly Thr Phe Val Leu
        770   775   780

Val Gln
785

<210>   15
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<212>   PRT
<213>   Homo sapiens

<400>   15

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1   5   10   15

Gly Gln Gln Lys Pro Leu Arg Val Gly Phe Tyr Asp Ile Glu Arg Thr

Leu Gly Lys Gly Asn Phe Ala Val Val Lys Leu Ala Arg His Arg Val
   35   40   45

Thr Lys Thr Gln Val Ala Ile Lys Ile Ile Asp Lys Thr Arg Leu Asp
  50   55   60

Ser Ser Asn Leu Glu Lys Ile Tyr Arg Glu Val Gln Leu Met Lys Leu
65   70   75   80

Leu Asn His Pro His Ile Ile Lys Leu Tyr Gln Val Met Glu Thr Lys
     85   90   95

Asp Met Leu Tyr Ile Val Thr Glu Phe Ala Lys Asn Gly Glu Met Phe
    100   105   110

Asp Tyr Leu Thr Ser Asn Gly His Leu Ser Glu Asn Glu Ala Arg Lys
   115   120   125

Lys Phe Trp Gln Ile Leu Ser Ala Val Glu Tyr Cys His Asp His His
  130   135   140

Ile Val His Arg Asp Leu Lys Thr Glu Asn Leu Leu Leu Asp Gly Asn
145   150   155   160

Met Asp Ile Lys Leu Ala Asp Phe Gly Phe Gly Asn Phe Tyr Lys Ser
    165   170   175

Gly Glu Pro Leu Ser Thr Trp Cys Gly Ser Pro Pro Tyr Ala Ala Pro
    180   185   190

Glu Val Phe Glu Gly Lys Glu Tyr Glu Gly Pro Gln Leu Asp Ile Trp
   195   200   205

Ser Leu Gly Val Val Leu Tyr Val Leu Val Cys Gly Ser Leu Pro Phe
  210   215   220

Asp Gly Pro Asn Leu Pro Thr Leu Arg Gln Arg Val Leu Glu Gly Arg
225   230   235   240

Phe Arg Ile Pro Phe Phe Met Ser Gln Asp Cys Glu Ser Leu Ile Arg
    245   250   255

Arg Met Leu Val Val Asp Pro Ala Arg Arg Ile Thr Ile Ala Gln Ile
    260   265   270

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Arg Gln His Arg Trp Met Arg Ala Glu Pro Cys Leu Pro Gly Pro Ala
        275             280             285

Cys Pro Ala Phe Ser Ala His Ser Tyr Thr Ser Asn Leu Gly Asp Tyr
    290             295             300

Asp Glu Gln Ala Leu Gly Ile Met Gln Thr Leu Gly Val Asp Arg Gln
305             310             315             320

Arg Thr Val Glu Ser Leu Gln Asn Ser Ser Tyr Asn His Phe Ala Ala
            325             330             335

Ile Tyr Tyr Leu Leu Leu Glu Arg Leu Lys Glu Tyr Arg Asn Ala Gln
            340             345             350

Cys Ala Arg Pro Gly Pro Ala Arg Gln Pro Arg Pro Arg Ser Ser Asp
        355             360             365

Leu Ser Gly Leu Glu Val Pro Gln Glu Gly Leu Ser Thr Asp Pro Phe
    370             375             380

Arg Pro Ala Leu Leu Cys Pro Gln Pro Gln Thr Leu Val Gln Ser Val
385             390             395             400

Leu Gln Ala Glu Met Asp Cys Glu Leu Gln Ser Ser Leu Gln Trp Pro
            405             410             415

Leu Phe Phe Pro Val Asp Ala Ser Cys Ser Gly Val Phe Arg Pro Arg
        420             425             430

Pro Val Ser Pro Ser Ser Leu Leu Asp Thr Ala Ile Ser Glu Glu Ala
        435             440             445

Arg Gln Gly Pro Gly Leu Glu Glu Glu Gln Asp Thr Gln Glu Ser Leu
    450             455             460

Pro Ser Ser Thr Gly Arg Arg His Thr Leu Ala Glu Val Ser Thr Arg
465             470             475             480

Leu Ser Pro Leu Thr Ala Pro Cys Ile Val Val Ser Pro Ser Thr Thr
            485             490             495

Ala Ser Pro Ala Glu Gly Thr Ser Ser Asp Ser Cys Leu Thr Phe Ser
        500             505             510

Ala Ser Lys Ser Pro Ala Gly Leu Ser Gly Thr Pro Ala Thr Gln Gly
    515             520             525
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Leu Leu Gly Ala Cys Ser Pro Val Arg Leu Ala Ser Pro Phe Leu Gly
    530   535   540

Ser Gln Ser Ala Thr Pro Val Leu Gln Ala Gln Gly Gly Leu Gly Gly
545   550   555   560

Ala Val Leu Leu Pro Val Ser Phe Gln Glu Gly Arg Arg Ala Ser Asp
                565   570   575

Thr Ser Leu Thr Gln Gly Leu Lys Ala Phe Arg Gln Gln Leu Arg Lys
            580   585   590

Thr Thr Arg Thr Lys Gly Phe Leu Gly Leu Asn Lys Ile Lys Gly Leu
            595   600   605

Ala Arg Gln Val Cys Gln Val Pro Ala Ser Arg Ala Ser Arg Gly Gly
    610   615   620

Leu Ser Pro Phe His Ala Pro Ala Gln Ser Pro Gly Leu His Gly Gly
625   630   635   640

Ala Ala Gly Ser Arg Glu Gly Trp Ser Leu Leu Glu Glu Val Leu Glu
                645   650   655

Gln Gln Arg Leu Leu Gln Leu Gln His His Pro Ala Ala Ala Pro Gly
            660   665   670

Cys Ser Gln Ala Pro Gln Pro Ala Pro Ala Pro Phe Val Ile Ala Pro
            675   680   685

Cys Asp Gly Pro Gly Ala Ala Pro Leu Pro Ser Thr Leu Leu Thr Ser
    690   695   700

Gly Leu Pro Leu Leu Pro Pro Pro Leu Leu Gln Thr Gly Ala Ser Pro
705   710   715   720

Val Ala Ser Ala Ala Gln Leu Leu Asp Thr His Leu His Ile Gly Thr
            725   730   735

Gly Pro Thr Ala Leu Pro Ala Val Pro Pro Pro Arg Leu Ala Arg Leu
            740   745   750

Ala Pro Gly Cys Glu Pro Leu Gly Leu Leu Gln Gly Asp Cys Glu Met
    755   760   765

Glu Asp Leu Met Pro Cys Ser Leu Gly Thr Phe Val Leu Val Gln
    770   775   780

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<212> PRT
<213> Homo sapiens

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Ala Ala Val Pro Ser Val Ser Leu Leu Ser Gly Ala Ser Ser Ser Ser
            20                  25                  30


Leu Ala Trp Cys Gly Leu Ala Thr Gly Ala Leu Gly Ala Gly Ala Arg
            35                  40                  45


Gly Ile Pro Glu Leu Arg Gly Ala Ala Gly Ala Gly Gly Ala Ala Gly
    50                  55                  60


Ala Gly Thr Gly Gly Ala Gly Pro Ala Gly Arg Leu Leu Pro Pro Pro
65                  70                  75                  80


Ala Pro Gly Ser Pro Ala Ala Pro Ala Ala Val Ser Pro Ala Ala Gly
            85                  90                  95


Gln Pro Arg Pro Pro Ala Pro Ala Ser Arg Gly Pro Met Pro Ala Arg
            100                 105                 110


Ile Gly Tyr Tyr Glu Ile Asp Arg Thr Ile Gly Lys Gly Asn Phe Ala
            115                 120                 125


Val Val Lys Arg Ala Thr His Leu Val Thr Lys Ala Lys Val Ala Ile
    130                 135                 140


Lys Ile Ile Asp Lys Thr Gln Leu Asp Glu Glu Asn Leu Lys Lys Ile
145                 150                 155                 160


Phe Arg Glu Val Gln Ile Met Lys Met Leu Cys His Pro His Ile Ile
            165                 170                 175


Arg Leu Tyr Gln Val Met Glu Thr Glu Arg Met Ile Tyr Leu Val Thr
            180                 185                 190


Glu Tyr Ala Ser Gly Gly Glu Ile Phe Asp His Leu Val Ala His Gly
            195                 200                 205


Arg Met Ala Glu Lys Glu Ala Arg Arg Lys Phe Lys Gln Ile Val Thr
    210                 215                 220
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Ala Val Tyr Phe Cys His Cys Arg Asn Ile Val His Arg Asp Leu Lys
225   230   235   240

Ala Glu Asn Leu Leu Leu Asp Ala Asn Leu Asn Ile Lys Ile Ala Asp
            245   250   255

Phe Gly Phe Ser Asn Leu Phe Thr Pro Gly Gln Leu Leu Lys Thr Trp
            260   265   270

Cys Gly Ser Pro Pro Tyr Ala Ala Pro Glu Leu Phe Glu Gly Lys Glu
            275   280   285

Tyr Asp Gly Pro Lys Val Asp Ile Trp Ser Leu Gly Val Val Leu Tyr
    290   295   300

Val Leu Val Cys Gly Ala Leu Pro Phe Asp Gly Ser Thr Leu Gln Asn
305   310   315   320

Leu Arg Ala Arg Val Leu Ser Gly Lys Phe Arg Ile Pro Phe Phe Met
            325   330   335

Ser Thr Glu Cys Glu His Leu Ile Arg His Met Leu Val Leu Asp Pro
            340   345   350

Asn Lys Arg Leu Ser Met Glu Gln Ile Cys Lys His Lys Trp Met Lys
            355   360   365

Leu Gly Asp Ala Asp Pro Asn Phe Asp Arg Leu Ile Ala Glu Cys Gln
    370   375   380

Gln Leu Lys Glu Glu Arg Gln Val Asp Pro Leu Asn Glu Asp Val Leu
385   390   395   400

Leu Ala Met Glu Asp Met Gly Leu Asp Lys Glu Gln Thr Leu Gln Ser
            405   410   415

Leu Arg Ser Asp Ala Tyr Asp His Tyr Ser Ala Ile Tyr Ser Leu Leu
            420   425   430

Cys Asp Arg His Lys Arg His Lys Thr Leu Arg Leu Gly Ala Leu Pro
            435   440   445

Ser Met Pro Arg Ala Leu Ala Phe Gln Ala Pro Val Asn Ile Gln Ala
    450   455   460

Glu Gln Ala Gly Thr Ala Met Asn Ile Ser Val Pro Gln Val Gln Leu

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465                    470                    475                    480

Ile Asn Pro Glu Asn Gln Ile Val Glu Pro Asp Gly Thr Leu Asn Leu
            485                490                495

Asp Ser Asp Glu Gly Glu Glu Pro Ser Pro Glu Ala Leu Val Arg Tyr
            500                505                510

Leu Ser Met Arg Arg His Thr Val Gly Val Ala Asp Pro Arg Thr Glu
            515                520                525

Val Met Glu Asp Leu Gln Lys Leu Leu Pro Gly Phe Pro Gly Val Asn
    530                535                540

Pro Gln Ala Pro Phe Leu Gln Val Ala Pro Asn Val Asn Phe Met His
545                550                555                560

Asn Leu Leu Pro Met Gln Asn Leu Gln Pro Thr Gly Gln Leu Glu Tyr
                565                570                575

Lys Glu Gln Ser Leu Leu Gln Pro Pro Thr Leu Gln Leu Leu Asn Gly
            580                585                590

Met Gly Pro Leu Gly Arg Arg Ala Ser Asp Gly Gly Ala Asn Ile Gln
            595                600                605

Leu His Ala Gln Gln Leu Leu Lys Arg Pro Arg Gly Pro Ser Pro Leu
    610                615                620

Val Thr Met Thr Pro Ala Val Pro Ala Val Thr Pro Val Asp Glu Glu
625                630                635                640

Ser Ser Asp Gly Glu Pro Asp Gln Glu Ala Val Gln Ser Ser Thr Tyr
            645                650                655

Lys Asp Ser Asn Thr Leu His Leu Pro Thr Glu Arg Phe Ser Pro Val
            660                665                670

Arg Arg Phe Ser Asp Gly Ala Ala Ser Ile Gln Ala Phe Lys Ala His
            675                680                685

Leu Glu Lys Met Gly Asn Asn Ser Ser Ile Lys Gln Leu Gln Gln Glu
    690                695                700

Cys Glu Gln Leu Gln Lys Met Tyr Gly Gly Gln Ile Asp Glu Arg Thr
705                710                715                720
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Leu Glu Lys Thr Gln Gln Gln His Met Leu Tyr Gln Gln Glu Gln His
              725   730   735

His Gln Ile Leu Gln Gln Gln Ile Gln Asp Ser Ile Cys Pro Pro Gln
              740   745   750

Pro Ser Pro Pro Leu Gln Ala Ala Cys Glu Asn Gln Pro Ala Leu Leu
         755   760   765

Thr His Gln Leu Gln Arg Leu Arg Ile Gln Pro Ser·Ser Pro Pro Pro
     770   775   780

Asn His Pro Asn Asn His Leu Phe Arg Gln Pro Ser Asn Ser Pro Pro
785   790   795   800

Pro Met Ser Ser Ala Met Ile Gln Pro His Gly Ala Ala Ser Ser Ser
              805   810   815

Gln Phe Gln Gly Leu Pro Ser Arg Ser Ala Ile Phe Gln Gln Gln Pro
              820   825   830

Glu Asn Cys Ser Ser Pro Pro Asn Val Ala Leu Thr Cys Leu Gly Met
         835   840   845

Gln Gln Pro Ala Gln Ser Gln Gln Val Thr Ile Gln Val Gln Glu Pro
     850   855   860

Val Asp Met Leu Ser Asn Met Pro Gly Thr Ala Ala Gly Ser Ser Gly
865   870   875   880

Arg Gly Ile Ser Ile Ser Pro Ser Ala Gly Gln Met Gln Met Gln His
              885   890   895

Arg Thr Asn Leu Met Ala Thr Leu Ser Tyr Gly His Arg Pro Leu Ser
         900   905   910

Lys Gln Leu Ser Ala Asp Ser Ala Glu Ala His Ser Leu Asn Val Asn
              915   920   925

Arg Phe Ser Pro Ala Asn Tyr Asp Gln Ala His Leu His Pro His Leu
     930   935   940

Phe Ser Asp Gln Ser Arg Gly Ser Pro Ser Ser Tyr Ser Pro Ser Thr
945   950   955   960

Gly Val Gly Phe Ser Pro Thr Gln Ala Leu Lys Val Pro Pro Leu Asp
              965   970   975

Page 42

Gln Phe Pro Thr Phe Pro Pro Ser Ala His Gln Gln Pro Pro His Tyr
       980   985   990

Thr Thr Ser Ala Leu Gln Gln Ala Leu Leu Ser Pro Thr Pro Pro Asp
       995   1000   1005

Tyr Thr Arg His Gln Gln Val Pro His Ile Leu Gln Gly Leu Leu
    1010   1015   1020

Ser Pro Arg His Ser Leu Thr Gly His Ser Asp Ile Arg Leu Pro
    1025   1030   1035

Pro Thr Glu Phe Ala Gln Leu Ile Lys Arg Gln Gln Gln Gln Arg
    1040   1045   1050

Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Glu Tyr Gln Glu Leu
    1055   1060   1065

Phe Arg His Met Asn Gln Gly Asp Ala Gly Ser Leu Ala Pro Ser
    1070   1075   1080

Leu Gly Gly Gln Ser Met Thr Glu Arg Gln Ala Leu Ser Tyr Gln
    1085   1090   1095

Asn Ala Asp Ser Tyr His His His Thr Ser Pro Gln His Leu Leu
    1100   1105   1110

Gln Ile Arg Ala Gln Glu Cys Val Ser Gln Ala Ser Ser Pro Thr
    1115   1120   1125

Pro Pro His Gly Tyr Ala His Gln Pro Ala Leu Met His Ser Glu
    1130   1135   1140

Ser Met Glu Glu Asp Cys Ser Cys Glu Gly Ala Lys Asp Gly Phe
    1145   1150   1155

Gln Asp Ser Lys Ser Ser Ser Thr Leu Thr Lys Gly Cys His Asp
    1160   1165   1170

Ser Pro Leu Leu Leu Ser Thr Gly Gly Pro Gly Asp Pro Glu Ser
    1175   1180   1185

Leu Leu Gly Thr Val Ser His Ala Gln Glu Leu Gly Ile His Pro
    1190   1195   1200

Tyr Gly His Gln Pro Thr Ala Ala Phe Ser Lys Asn Lys Val Pro
    1205   1210   1215

Ser Arg Glu Pro Val Ile Gly Asn Cys Met Asp Arg Ser Ser Pro
    1220   1225   1230

Gly Gln Ala Val Glu Leu Pro Asp His Asn Gly Leu Gly Tyr Pro
    1235   1240   1245

Ala Arg Pro Ser Val His Glu His His Arg Pro Arg Ala Leu Gln
    1250   1255   1260

Arg His His Thr Ile Gln Asn Ser Asp Asp Ala Tyr Val Gln Leu
    1265   1270   1275

Asp Asn Leu Pro Gly Met Ser Leu Val Ala Gly Lys Ala Leu Ser
    1280   1285   1290

Ser Ala Arg Met Ser Asp Ala Val Leu Ser Gln Ser Ser Leu Met
    1295   1300   1305

Gly Ser Gln Gln Phe Gln Asp Gly Glu Asn Glu Glu Cys Gly Ala
    1310   1315   1320

Ser Leu Gly Gly His Glu His Pro Asp Leu Ser Asp Gly Ser Gln
    1325   1330   1335

His Leu Asn Ser Ser Cys Tyr Pro Ser Thr Cys Ile Thr Asp Ile
    1340   1345   1350

Leu Leu Ser Tyr Lys His Pro Glu Val Ser Phe Ser Met Glu Gln
    1355   1360   1365

Ala Gly Val
    1370

<210> 17
<211> 926
<212> PRT
<213> Homo sapiens

<400> 17

Met Val Met Ala Asp Gly Pro Arg His Leu Gln Arg Gly Pro Val Arg
1   5   10   15

Val Gly Phe Tyr Asp Ile Glu Gly Thr Leu Gly Lys Gly Asn Phe Ala
            20   25   30

Val Val Lys Leu Gly Arg His Arg Ile Thr Lys Thr Glu Val Ala Ile
        35   40   45

Lys Ile Ile Asp Lys Ser Gln Leu Asp Ala Val Asn Leu Glu Lys Ile
   50   55   60

Tyr Arg Glu Val Gln Ile Met Lys Met Leu Asp His Pro His Ile Ile
65   70   75   80

Lys Leu Tyr Gln Val Met Glu Thr Lys Ser Met Leu Tyr Leu Val Thr
         85   90   95

Glu Tyr Ala Lys Asn Gly Glu Ile Phe Asp Tyr Leu Ala Asn His Gly
         100   105   110

Arg Leu Asn Glu Ser Glu Ala Arg Arg Lys Phe Trp Gln Ile Leu Ser
         115   120   125

Ala Val Asp Tyr Cys His Gly Arg Lys Ile Val His Arg Asp Leu Lys
      130   135   140

Ala Glu Asn Leu Leu Leu Asp Asn Asn Met Asn Ile Lys Ile Ala Asp
145   150   155   160

Phe Gly Phe Gly Asn Phe Phe Lys Ser Gly Glu Leu Leu Ala Thr Trp
         165   170   175

Cys Gly Ser Pro Pro Tyr Ala Ala Pro Glu Val Phe Glu Gly Gln Gln
         180   185   190

Tyr Glu Gly Pro Gln Leu Asp Ile Trp Ser Met Gly Val Val Leu Tyr
         195   200   205

Val Leu Val Cys Gly Ala Leu Pro Phe Asp Gly Pro Thr Leu Pro Ile
      210   215   220

Leu Arg Gln Arg Val Leu Glu Gly Arg Phe Arg Ile Pro Tyr Phe Met
225   230   235   240

Ser Glu Asp Cys Glu His Leu Ile Arg Arg Met Leu Val Leu Asp Pro
         245   250   255

Ser Lys Arg Leu Thr Ile Ala Gln Ile Lys Glu His Lys Trp Met Leu
         260   265   270

Ile Glu Val Pro Val Gln Arg Pro Val Leu Tyr Pro Gln Glu Gln Glu
         275   280   285

Asn Glu Pro Ser Ile Gly Glu Phe Asn Glu Gln Val Leu Arg Leu Met

290   295   300

His Ser Leu Gly Ile Asp Gln Gln Lys Thr Ile Glu Ser Leu Gln Asn
305   310   315   320

Lys Ser Tyr Asn His Phe Ala Ala Ile Tyr Phe Leu Leu Val Glu Arg
                325   330   335

Leu Lys Ser His Arg Ser Ser Phe Pro Val Glu Gln Arg Leu Asp Gly
            340   345   350

Arg Gln Arg Arg Pro Ser Thr Ile Ala Glu Gln Thr Val Ala Lys Ala
        355   360   365

Gln Thr Val Gly Leu Pro Val Thr Met His Ser Pro Asn Met Arg Leu
    370   375   380

Leu Arg Ser Ala Leu Leu Pro Gln Ala Ser Asn Val Glu Ala Phe Ser
385   390   395   400

Phe Pro Ala Ser Gly Cys Gln Ala Glu Ala Ala Phe Met Glu Glu Glu
                405   410   415

Cys Val Asp Thr Pro Lys Val Asn Gly Cys Leu Leu Asp Pro Val Pro
            420   425   430

Pro Val Leu Val Arg Lys Gly Cys Gln Ser Leu Pro Ser Asn Met Met
        435   440   445

Glu Thr Ser Ile Asp Glu Gly Leu Glu Thr Glu Gly Glu Ala Glu Glu
    450   455   460

Asp Pro Ala His Ala Phe Glu Ala Phe Gln Ser Thr Arg Ser Gly Gln
465   470   475   480

Arg Arg His Thr Leu Ser Glu Val Thr Asn Gln Leu Val Val Met Pro
            485   490   495

Gly Ala Gly Lys Ile Phe Ser Met Asn Asp Ser Pro Ser Leu Asp Ser
            500   505   510

Val Asp Ser Glu Tyr Asp Met Gly Ser Val Gln Arg Asp Leu Asn Phe
        515   520   525

Leu Glu Asp Asn Pro Ser Leu Lys Asp Ile Met Leu Ala Asn Gln Pro
    530   535   540

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Ser Pro Arg Met Thr Ser Pro Phe Ile Ser Leu Arg Pro Thr Asn Pro
545   550   555   560

Ala Met Gln Ala Leu Ser Ser Gln Lys Arg Glu Val His Asn Arg Ser
             565   570   575

Pro Val Ser Phe Arg Glu Gly Arg Arg Ala Ser Asp Thr Ser Leu Thr
             580   585   590

Gln Gly Ile Val Ala Phe Arg Gln His Leu Gln Asn Leu Ala Arg Thr
             595   600   605

Lys Gly Ile Leu Glu Leu Asn Lys Val Gln Leu Leu Tyr Glu Gln Ile
    610   615   620

Gly Pro Glu Ala Asp Pro Asn Leu Ala Pro Ala Ala Pro Gln Leu Gln
625   630   635   640

Asp Leu Ala Ser Ser Cys Pro Gln Glu Glu Val Ser Gln Gln Gln Glu
             645   650   655

Ser Val Ser Thr Leu Pro Ala Ser Val His Pro Gln Leu Ser Pro Arg
             660   665   670

Gln Ser Leu Glu Thr Gln Tyr Leu Gln His Arg Leu Gln Lys Pro Ser
             675   680   685

Leu Leu Ser Lys Ala Gln Asn Thr Cys Gln Leu Tyr Cys Lys Glu Pro
    690   695   700

Pro Arg Ser Leu Glu Gln Gln Leu Gln Glu His Arg Leu Gln Gln Lys
705   710   715   720

Arg Leu Phe Leu Gln Lys Gln Ser Gln Leu Gln Ala Tyr Phe Asn Gln
             725   730   735

Met Gln Ile Ala Glu Ser Ser Tyr Pro Gln Pro Ser Gln Gln Leu Pro
             740   745   750

Leu Pro Arg Gln Glu Thr Pro Pro Pro Ser Gln Gln Ala Pro Pro Phe
             755   760   765

Ser Leu Thr Gln Pro Leu Ser Pro Val Leu Glu Pro Ser Ser Glu Gln
    770   775   780

Met Gln Tyr Ser Pro Phe Leu Ser Gln Tyr Gln Glu Met Gln Leu Gln
785   790   795   800

Pro Leu Pro Ser Thr Ser Gly Pro Arg Ala Ala Pro Pro Leu Pro Thr
            805   810   815

Gln Leu Gln Gln Gln Gln Pro Pro Pro Pro Pro Pro Pro Pro Pro Pro
            820   825   830

Arg Gln Pro Gly Ala Ala Pro Ala Pro Leu Gln Phe Ser Tyr Gln Thr
            835   840   845

Cys Glu Leu Pro Ser Ala Ala Ser Pro Ala Pro Asp Tyr Pro Thr Pro
    850   855   860

Cys Gln Tyr Pro Val Asp Gly Ala Gln Gln Ser Asp Leu Thr Gly Pro
865   870   875   880

Asp Cys Pro Arg Ser Pro Gly Leu Gln Glu Ala Pro Ser Ser Tyr Asp
            885   890   895

Pro Leu Ala Leu Ser Glu Leu Pro Gly Leu Phe Asp Cys Glu Met Leu
            900   905   910

Asp Ala Val Asp Pro Gln His Asn Gly Tyr Val Leu Val Asn
            915   920   925

<210>   18
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<400>   18

Met Val Met Ala Asp Gly Pro Arg His Leu Gln Arg Gly Pro Val Arg
1   5   10   15

Val Gly Phe Tyr Asp Ile Glu Gly Thr Leu Gly Lys Gly Asn Phe Ala
            20   25   30

Val Val Lys Leu Gly Arg His Arg Ile Thr Lys Thr Glu Val Ala Ile
            35   40   45

Lys Ile Ile Asp Lys Ser Gln Leu Asp Ala Val Asn Leu Glu Lys Ile
    50   55   60

Tyr Arg Glu Val Gln Ile Met Lys Met Leu Asp His Pro His Ile Ile
65   70   75   80

Lys Leu Tyr Gln Val Met Glu Thr Lys Ser Met Leu Tyr Leu Val Thr
            85   90   95

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Glu Tyr Ala Lys Asn Gly Glu Ile Phe Asp Tyr Leu Ala Asn His Gly
            100   105   110

Arg Leu Asn Glu Ser Glu Ala Arg Arg Lys Phe Trp Gln Ile Leu Ser
            115   120   125

Ala Val Asp Tyr Cys His Gly Arg Lys Ile Val His Arg Asp Leu Lys
            130   135   140

Ala Glu Asn Leu Leu Leu Asp Asn Asn Met Asn Ile Lys Ile Ala Asp
145   150   155   160

Phe Gly Phe Gly Asn Phe Phe Lys Ser Gly Glu Leu Leu Ala Thr Trp
            165   170   175

Cys Gly Ser Pro Pro Tyr Ala Ala Pro Glu Val Phe Glu Gly Gln Gln
            180   185   190

Tyr Glu Gly Pro Gln Leu Asp Ile Trp Ser Met Gly Val Val Leu Tyr
            195   200   205

Val Leu Val Cys Gly Ala Leu Pro Phe Asp Gly Pro Thr Leu Pro Ile
210   215   220

Leu Arg Gln Arg Val Leu Glu Gly Arg Phe Arg Ile Pro Tyr Phe Met
225   230   235   240

Ser Glu Asp Cys Glu His Leu Ile Arg Arg Met Leu Val Leu Asp Pro
            245   250   255

Ser Lys Arg Leu Thr Ile Ala Gln Ile Lys Glu His Lys Trp Met Leu
            260   265   270

Ile Glu Val Pro Val Gln Arg Pro Val Leu Tyr Pro Gln Glu Gln Glu
            275   280   285

Asn Glu Pro Ser Ile Gly Glu Phe Asn Glu Gln Val Leu Arg Leu Met
            290   295   300

His Ser Leu Gly Ile Asp Gln Gln Lys Thr Ile Glu Ser Leu Gln Asn
305   310   315   320

Lys Ser Tyr Asn His Phe Ala Ala Ile Tyr Phe Leu Leu Val Glu Arg
            325   330   335

Leu Lys Ser His Arg Ser Ser Phe Pro Val Glu Gln Arg Leu Asp Gly
            340   345   350

Arg Gln Arg Arg Pro Ser Thr Ile Ala Glu Gln Thr Val Ala Lys Ala
    355   360   365

Gln Thr Val Gly Leu Pro Val Thr Met His Ser Pro Asn Met Arg Leu
    370   375   380

Leu Arg Ser Ala Leu Leu Pro Gln Ala Ser Asn Val Glu Ala Phe Ser
385   390   395   400

Phe Pro Ala Ser Gly Cys Gln Ala Glu Ala Ala Phe Met Glu Glu Glu
            405   410   415

Cys Val Asp Thr Pro Lys Val Asn Gly Cys Leu Leu Asp Pro Val Pro
        420   425   430

Pro Val Leu Val Arg Lys Gly Cys Gln Ser Leu Pro Ser Asn Met Met
      435   440   445

Glu Thr Ser Ile Asp Glu Gly Leu Glu Thr Glu Gly Glu Ala Glu Glu
    450   455   460

Asp Pro Ala His Ala Phe Glu Ala Phe Gln Ser Thr Arg Ser Gly Gln
465   470   475   480

Arg Arg His Thr Leu Ser Glu Val Thr Asn Gln Leu Val Val Met Pro
            485   490   495

Gly Ala Gly Lys Ile Phe Ser Met Asn Asp Ser Pro Ser Leu Asp Ser
        500   505   510

Val Asp Ser Glu Tyr Asp Met Gly Ser Val Gln Arg Asp Leu Asn Phe
        515   520   525

Leu Glu Asp Asn Pro Ser Leu Lys Asp Ile Met Leu Ala Asn Gln Pro
    530   535   540

Ser Pro Arg Met Thr Ser Pro Phe Ile Ser Leu Arg Pro Thr Asn Pro
545   550   555   560

Ala Met Gln Ala Leu Ser Ser Gln Lys Arg Glu Val His Asn Arg Ser
        565   570   575

Pro Val Ser Phe Arg Glu Gly Arg Arg Ala Ser Asp Thr Ser Leu Thr
        580   585   590

Gln Gly Ile Val Ala Phe Arg Gln His Leu Gln Asn Leu Ala Arg Thr

             595   600   605

Lys Gly Ile Leu Glu Leu Asn Lys Val Gln Leu Leu Tyr Glu Gln Ile
    610   615   620

Gly Pro Glu Ala Asp Pro Asn Leu Ala Pro Ala Ala Pro Gln Leu Gln
625   630   635   640

Asp Leu Ala Ser Ser Cys Pro Gln Glu Glu Val Ser Gln Gln Gln Glu
                645   650   655

Ser Val Ser Thr Leu Pro Ala Ser Val His Pro Gln Leu Ser Pro Arg
                660   665   670

Gln Ser Leu Glu Thr Gln Tyr Leu Gln His Arg Leu Gln Lys Pro Ser
                675   680   685

Leu Leu Ser Lys Ala Gln Asn Thr Cys Gln Leu Tyr Cys Lys Glu Pro
    690   695   700

Pro Arg Ser Leu Glu Gln Gln Leu Gln Glu His Arg Leu Gln Gln Lys
705   710   715   720

Arg Leu Phe Leu Gln Lys Gln Ser Gln Leu Gln Ala Tyr Phe Asn Gln
                725   730   735

Met Gln Ile Ala Glu Ser Ser Tyr Pro Gln Pro Ser Gln Gln Leu Pro
                740   745   750

Leu Pro Arg Gln Glu Thr Pro Pro Pro Ser Gln Gln Ala Pro Pro Phe
    755   760   765

Ser Leu Thr Gln Pro Leu Ser Pro Val Leu Glu Pro Ser Ser Glu Gln
    770   775   780

Met Gln Tyr Ser Pro Phe Leu Ser Gln Tyr Gln Glu Met Gln Leu Gln
785   790   795   800

Pro Leu Pro Ser Thr Ser Gly Pro Arg Ala Ala Pro Pro Leu Pro Thr
                805   810   815

Gln Leu Gln Gln Gln Gln Pro Pro Pro Pro Pro Pro Pro Pro Pro Pro
                820   825   830

Arg Gln Pro Gly Ala Ala Pro Ala Pro Leu Gln Phe Ser Tyr Gln Thr
    835   840   845

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```
Cys Glu Leu Pro Ser Ala Ala Ser Pro Ala Pro Asp Tyr Pro Thr Pro
    850             855             860
```

```
Cys Gln Tyr Pro Val Asp Gly Ala Gln Gln Ser Asp Leu Thr Gly Pro
865             870             875             880
```

```
Asp Cys Pro Arg Ser Pro Gly Leu Gln Glu Ala Pro Ser Ser Tyr Asp
            885             890             895
```

```
Pro Leu Ala Leu Ser Glu Leu Pro Gly Leu Phe Asp Cys Glu Met Leu
            900             905             910
```

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Asp Ala Val Asp Pro Gln His Asn Gly Tyr Val Leu Val Asn
    915             920             925
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